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Recent Advances in the Immunopathogenesis of Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a chronic multisystem inflammatory disease having definite etiologic associations with ethnic, genetic, viral and immunologic factors. Its pathologic hallmark, vasculitis, is currently felt to be the end result of an immune-complex mechanism. Several clinical and serologic variants of SLE are recognized including discoid lupus erythematosus (DLE), mixed connective tissue disease (MCTD) and drug-induced equivalents —such as procainamide-induced lupus (PIL). The distinguishing features of these variants as well as their prognosis and therapy are discussed in relation to recent developments in the immunopathogenesis of SLE.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is an immunologically mediated disease characterized by multisystem involvement and a capricious tendency to undergo remissions and exacerbations. The increase in prevalence of this disease has been attributed to its earlier recognition and the longer survival of patients.[1] The disease is more frequent in women of childbearing age, occurring five to six times more commonly in females than in males. A recent epidemiological study comparing the incidence, prevalence, and mortality of SLE showed that the risk of this disease was three times greater in black females than in white females.[1] Increased incidence in blacks was not related to unfavorable socioeconomic conditions, but was attributed to a fundamental defect in the immune response.

Since the discovery of the LE cell in bone marrow preparations by Hargraves in 1948, evidence has accumulated implicating immune mechanisms in the renal and vascular lesions of this disease. Despite improved understanding of this entity, confusion persists concerning the clinical and serologic discrimination of several lupus variants. This review deals with recent developments relating to the immunopathogenesis of SLE and considers clinical and serologic variations among the lupus variants as well as developments relating to their treatment.

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Etiologic Factors

Extensive genetic, viral, serologic and histopathologic investigations have suggested a multifactorial cause contributing to the immunologic abnormalities in SLE.

Genetic Aspects

A definite familial occurrence of SLE has been observed.[2,3] Increased gammaglobulin, antinuclear antibodies and other immunological aberrations have been observed in first degree relatives of patients with SLE.[1-4] Studies of the possible relationship between specific histocompatibility antigens and SLE have produced diverse findings. A variety of HL-A antigens* (A5, A7, A8, A13, W5, W15 and an X type) have been observed in association with an increased risk of developing the disease.[5-11] Whether these observations are merely artifacts attributable to chance, or indeed related to SLE is unclear. A severe C2 complement deficiency, perhaps inherited, has been associated with an increased incidence of infection and a lupus-like syndrome. This suggests another genetic pathway in the development of SLE.[12,13] C2 deficiency is felt to increase host susceptibility to infection, particularly chronic viral infection. In this setting, immunization against deoxyribonucleic acid (DNA) might occur more rapidly with development of clinical SLE.

Virus Association

The role of viral infection as a potential etiologic factor, as a contributor to soluble immune complex formation and as an immunogen for certain antibodies found in sera of SLE patients has been extensively investigated.[14-29] Cytoplasmic inclusions resembling the nucleocapsid of paramyxovirus have been observed in the skin and kidney of patients with SLE.[14-18] However, attempts to culture viruses from specimens showing intracellular inclusions failed to demonstrate an active agent.[19] It is currently felt that these tubular structures represent a cellular reaction to viral infection rather than the actual nucleocapsid of a virus.[20] These initial observations fostered a series of studies for circulating antibodies against virus strains in sera of SLE subjects. Initially, two paramyxoviruses, measles and parainfluenza-1, were found to have a high association to SLE by virtue of higher serum antibody levels.[21,22] Unlike the nonspecific observations with intracellular tubular structures, other connective tissue disorders do not demonstrate similar levels of increased antibody to these viruses.[23]

Further studies implicate other viruses to SLE (such as respiratory syncytial, herpes virus, rubella, parainfluenza-2 and -3, reovirus-2, Epstein-Barr virus and hepatitis-associated antigen).[24,25] Recently, Rothfield and associates have suggested that chronic Epstein-Barr virus infection, secondary to impaired cellular immunity, may be an important etiological factor in certain patients with SLE.[27] Sensitive radioimmunoassays have demonstrated antibodies to reovirus double stranded ribonucleic acid (ds-RNA) both in patients with SLE and in New Zealand Black and New Zealand White (NZB, NZW) mice.[28,29] There is no significant amount of ds-RNA in normal mammalian cells. Since the only recognized naturally occurring ds-RNA's are the replicative forms of RNA viruses, it is tempting to speculate that such a virus infection may be responsible for the development of these antibodies in patients with SLE.

Genetic-Viral Interactions

The roles of both viral and genetic factors have become well established in both murine and canine lupus.[30-32] In NZB mice, the lupus diathesis depends on a genetically determined hyperreactivity to nuclear antigens, with a superimposed viral infection to activate this responsiveness.[30] Mating experiments with affected dogs suggests the presence of a transmissible agent in first filial generation puppies.[31] In recent experiments, cell free filtrates prepared from spleens of SLE dogs were injected into normal newborn dogs and mice. This resulted in the induction of serologic abnormalities in the injected animals.[32] Canine recipients developed antinuclear antibodies and positive LE cell phenomena. In some murine recipients anti-DNA antibody was also produced. Many of the latter subsequently developed a viral-induced lymphoma. These results suggest that the SLE canine donors possess a virus capable of inducing the serologic abnormalities of SLE in normal dogs and mice, as well as activation of a latent murine leukemia virus.

The close association of genetic and viral influences in murine, canine and human SLE, and the relationship of disease exacerbations to a variety of drugs, trauma, infection or exposure to sunlight, suggest an etiologic parallel to the

*Histocompatibility antigens on the surface of nucleated cells determined by a single major chromosomal locus, the HL-A locus.

current theories of viral oncogenesis in human leukemia.[33]

Immunopathologic Features

A consistent, characteristic feature of SLE is the presence of numerous serologic abnormalities, including a wide variety of antibodies directed against nuclear, cytoplasmic and serum protein antigens.[34] Anti-lymphocyte, anti-thrombocyte, anti-erythrocyte and anti-clotting factor antibodies may result in leukopenia, thrombocytopenia, hemolytic anemia or an overt hemorraghic diathesis, respectively.[35-40]

Deoxyribonucleic Acid

Antibodies to purified native DNA were recognized early in the study of the serology of SLE.[41] An important early distinction made was that there are two major antigens; native or double stranded DNA (ds-DNA) and denatured or single stranded DNA (ss-DNA). Antibodies present in sera of patients with SLE were found to be heterogeneous and directed against a variety of determinants in both double and single stranded DNA.[42-45] The importance of this distinction is that antibody to ss-DNA, though almost universally present in SLE, occurs with a broader spectrum of immunologically mediated disease.[45] Both ds-DNA and ss-DNA have been found to alternate with the presence of their respective circulating antibodies in SLE sera.[43] However, ss-DNA occurs with greater frequency in the highest concentrations in sera of patients with SLE.[46] It has been proposed that ss-DNA may be the immunogen for the circulating DNA:anti-DNA complexes which play a vital role in the pathogenesis of lupus nephritis.

Deoxyribonucleoprotein

A third group of antibodies involving DNA are directed against nucleoprotein and require both DNA and protein moieties for their interaction. The active principle in SLE serum responsible for the development of the LE cell phenomenon appears to be mediated by antibodies to deoxyribonucleoprotein.[47] Recent studies employing sensitive primary binding techniques demonstrated that the majority of sera from SLE patients contained antibodies to both soluble nucleoprotein and native DNA and that increased levels of antinucleoprotein antibody paralleled renal disease activity.[48] The source of DNA in the serum of SLE patients remains unknown, although a viral or bacterial origin cannot be entirely excluded. The large concentrations, particularly of ss-DNA, suggest an endogenous origin.

Ribosomes and Ribonucleic Acid

Antibodies to cytoplasmic antigens have also been described. Antibodies to ribosomes occur in a small proportion of SLE patients who usually have severe renal disease.[49] An interesting development in the serology of SLE was the discovery of antibodies to ds-RNA, as well as to RNA-DNA hybrids.[50,51] Interest in these antibodies goes beyond their diagnostic specificity and extends into their possible etiologic relationship to SLE. Antibodies against ds-RNA have been observed during peaks of disease activity, but are also present during clinically inactive periods with no relationship to clinical activity.[52]

Precipitating Antibodies

Agar diffusion techniques have permitted investigators to identify four additional antigenic specificities against which SLE sera often contain antibodies.[53] Antibodies to a soluble, nuclear, non-nucleic acid called Sm protein are confined almost exclusively to SLE sera and occur in 30 to 40 percent of cases.[54] Antibodies to another soluble moiety, similar to Sm but cytoplasmic in origin and called Ro, are seen in 30 percent of SLE sera, but rarely together with anti-Sm antibodies.[55] A small proportion of SLE patients with anti-Ro have been noted not to have antinuclear antibodies. Two additional nuclear and cytoplasmic RNA-protein antigens, Mo and La, have been described.[56-57] The nuclear RNA-protein antigen called Mo is probably related to the RNAse susceptible portion of extractable nuclear antigen (ENA) isolated by Sharp and associates.[58,59] ENA probably represents a composite of the Mo and Sm antigens. Assays using the ENA antigen moiety therefore measure anti-Mo or anti-Sm antibodies in the serum.[34] There appears to be a negative association between anti-Mo and anti-DNA antibodies in SLE sera.

Bovine Serum Proteins

Other antigen-antibody systems have been noted in the sera of SLE patients, therefore supporting the speculation that this syndrome may be the end result of several different immune complex mechanisms. The possibility that ingested antigens are playing some role in the pathogenesis of

SLE received support by the observation of increased antibody activity directed against bovine gammaglobulin (BGG) and albumin (BSA).[60] This hypothesis was strengthened by the presence of a BGG-like material in several SLE sera, and in one case, the coexistence of this material and anti-BGG.[60] A high incidence of anti-bovine immunoglobulin M (IgM) also has been found in the sera of immunoglobulin A (IgA) deficient patients.[61] Serum IgA deficiency has been reported with greater than normal frequency in SLE patients.[62] It is possible that loss of secretory IgA, or other gastrointestinal protective mechanisms, permits a greater concentration of antigenically intact molecules to enter the circulation of these genetically predisposed persons. Recently, a patient was described in whom LE cells, tart cells, antibody to ENA, and reduced serum C3 developed on oral milk challenge.[63] The patient's serum also contained milk-precipitating antibodies.

Cryoproteins

Sera of many SLE patients contains immunoglobulins which precipitate in the cold. These cryoproteins consist of complexes of IgM, immunoglobulin G (IgG) and complement components. They occur during the acute or active phases of the disease and are associated with low levels of serum complement.[64] Whether they play an active role in the pathogenesis of lupus nephritis has not been resolved. An antibody-like material directed toward a thermolabile serum macroprotein, distinguishable from C1q, was recently described in SLE sera.[65] It is associated with disease activity and may represent another system involved in the pathogenesis of SLE.

Immune Complexes

Serological studies therefore suggest the presence of a variety of immune complexes in sera of SLE patients. These immune complexes play a major role in the induction of vasculitis, the pathologic hallmark of SLE.

Kidney

The presence of gammaglobulin, complement and fibrinogen in the glomerular lesions of patients with SLE has been shown by immunohistological techniques.[66,67] Three major patterns of immunoglobulin and complement deposition are generally appreciated (linear, mesangial and granular).[68] Linear deposits of IgG without concurrent localization of complement have been observed in a small proportion of patients. Mesangial deposits are usually found in a characteristic pattern of irregular, homogeneous strands of protein lying between capillary loops. The linear or mesangial patterns are usually not associated with clinical or histological evidence of renal disease. Granular deposits are of two types. In most cases, they are irregular in size and distribution throughout the glomerulus. In a few patients with membranous glomerulonephritis, a fine homogeneous granular deposition may be observed.

The direct participation of circulating immune complexes in the induction of nephritis is supported by the fact that gammaglobulin eluted from involved glomeruli contains a higher proportion of antinuclear and anti-DNA activity than does circulating gammaglobulin.[69] Further proof was provided by the detection of DNA and anti-DNA in the glomerular deposits[69] as well as in the circulation,[43] and by the association of active renal disease with the presence of circulating DNA:anti-DNA complexes and hypocomplementemia.[70,71]

Studies employing semiquantitative electron microscopic and immunohistologic methods demonstrated a relationship between increasing amounts of subendothelial and mesangial deposits.[72] Subendothelial deposits were found only in active renal disease, and were extensive only in the presence of large mesangial deposits. There was an unexpected inverse relationship between the extent of subendothelial and subepithelial deposits. The former were found only with the most active histologic changes, carried a poor prognosis and tended to disappear with time and treatment. On the other hand, subepithelial and intramembranous deposits were not necessarily related to active renal disease, carried an excellent prognosis and tended to persist for long periods of time unrelated to treatment. This appears to substantiate the observations that in almost all SLE patients there is glomerular pathology whether or not clinical nephritis is apparent.[73,74]

Skin

Antibodies, usually of an IgG type, may be found in the skin lesions of as many as 90 percent of patients with SLE and in clinically normal skin of 60 percent of such patients.[75] These antibodies appear in a coarse granular pattern at the dermal-epidermal junction and are felt to represent immune complex deposition similar to that observed in glomerular basement membranes

(GBM). Studies of the acid eluates from both glomeruli and normal-appearing skin of three patients with SLE showed that these eluates contained antinuclear antibodies.[76] These antinuclear antibodies demonstrated anti-DNA or anti-ENA specificity, fixed complement, and were deposited in skin in proportion to the total serum IgG concentration. In two of the three cases, a basement membrane antibody was observed that fixed complement and gave a linear fluorescent pattern. These observations have important pathogenic and clinical implications. Both skin[76] and GBM[68,76] are affected by an immune complex, as well as a separate anti-basement membrane antibody mechanism. Furthermore, careful studies of normal and involved skin in SLE patients may reflect to a large extent what is present in the kidney and may obviate the risks of renal biopsy.[77,78]

Central Nervous System

Central nervous system (CNS) disease in lupus appears to be associated with vasculitis involving small blood vessels.[79] Necrosis, thrombi and proliferative changes in arterioles and capillaries have been found to occur with microinfarcts. Considerable evidence exists to support the contention that CNS lupus is also mediated by soluble immune complexes associated with activated components of the complement system.[71,80-86]

Complement

Total hemolytic complement levels are depressed at some time in most patients with systemic lupus erythematosus, while levels are generally normal in patients with discoid lupus.[87] Analysis of complement components in sera from patients with active SLE has demonstrated low levels of C1q, C1s, C4, C2 and C3, although C5 levels were reported as normal.[88,89] These low levels of complement are presumed to reflect complement fixation by immune complexes forming in the circulation and being deposited in certain tissues. SLE sera with low complement levels has been found to be anti-complementary secondary to a high molecular weight fraction containing gammaglobulin, presumably either as aggregates of gammaglobulin or of immune complexes. Highly purified C1q, which readily precipitates in gel diffusion with immune complexes or aggregates of gammaglobulin, has been shown to precipitate with hypocomplementemic lupus sera.[90]

Recent studies have provided evidence to implicate the alternate pathway of the complement system in the pathogenesis of some cases of SLE.[91,92] C3 proactivator is notably decreased in active lupus. There is an excellent correlation between serum C3 and C3 proactivator. Serum properdin levels are also decreased in active disease, and may be participating in the development of lupus nephritis. It is of interest that 20 percent of a group of patients with SLE were found to have properdin deposited along the skin basement membrane associated with C1q, C4, C3, C5 and immunoglobulins.[93] C3 proactivator was observed in the skin of fewer persons.

Cell-Mediated Immunity

Developments in humorally-mediated events of SLE have been presented to substantiate their apparent major role in mediating tissue damage. However, some exciting developments have evolved to implicate an alteration in cellular immune mechanisms in the mediation of this disease syndrome. A variety of studies have indicated that lymphocytotoxic antibody activity is present in the sera of patients with SLE.[35,36,94] These antibodies appear to have T-cell, and possibly HL-A, specificity.[36] A relative and absolute decrease in T-lymphocytes and cells bearing a receptor for C3 has been reported in active lupus.[94] The absolute number of cells bearing surface immunoglobulin was slightly reduced, whereas the proportion of these cells was increased. There is sufficient evidence to postulate that the increased numbers of autoantibodies and the depressed delayed hypersensitivity seen in SLE is due to a decrease in T-lymphocyte function. This hypothesis is supported by a study comparing humoral and cellular immune reactivity to DNA in patients with SLE.[95]

Immunopathologic Summary

A schematic presentation of a possible sequence of steps leading to the induction of SLE is shown in Figure 1. It is believed that a variety of genetic factors predispose persons to the future development of this condition. Superimposed on this genetic endowment, the development of chronic viral infection appears to be an equally important participant in its pathogenesis. The interaction between cell-incorporated viral DNA and a variety of potential subsequent infectious agents, chemical trauma or physical trauma may result in destruc-

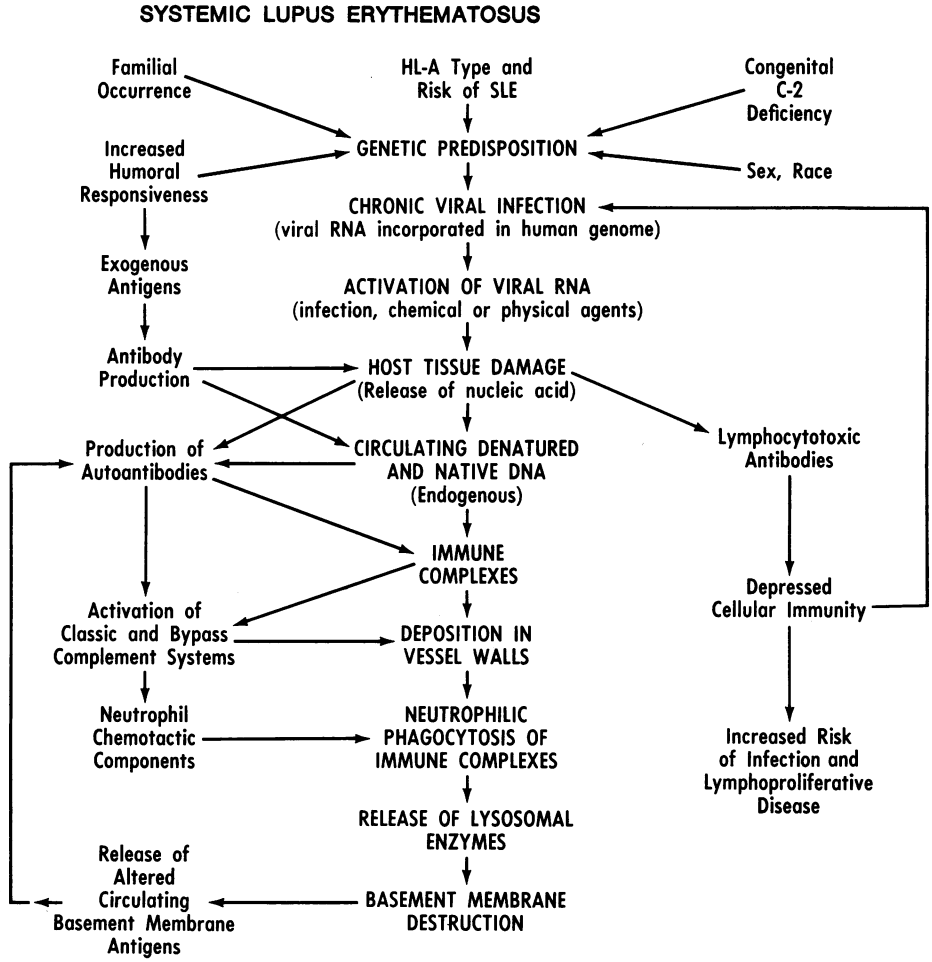

Figure 1.—A schematic presentation of a hypothetical sequence of events leading to the induction of systemic lupus erythematosus.

tion of host tissue with release of nucleic acid materials, in particular ss-DNA, into the circulation. The congenital tendency to increased humoral responsiveness results in the production of a spectrum of autoantibodies against both nucleic and cytoplasmic antigens with the subsequent formation of circulating immune complexes. Exogenous nucleic acids and other foreign substances may also contribute to this humoral response. Circulating immune complexes activate the complement cascade system with the generation of neutrophilic chemotactic components. The immune complexes and activated components of the complement system are deposited on vascular endothelium. The influx of phagocytic polymorphonuclear cells undergoes destruction by terminal components of complement, with release of lysosomal enzymes which inflict damage on the endothelium. Release into the circulation of altered basement membrane antigens may then act as a self-perpetuating system to induce cytotoxic antibodies which may further interact with basement membrane. Autoantibodies directed against T-lymphocytes inhibit cell-mediated immunity, and accentuate the vulnerability of these patients to a variety of viral infections and the earlier development of malignancy.

Clinical Variants

In the last decade, major advances in the immunopathogenesis of SLE have stimulated a reappraisal of the relationship among SLE, discoid lupus erythematosus (DLE) and drug-induced equivalents of SLE—such as procainamide-induced lupus (PIL). Moreover, recent observations by Sharp and associates suggest the existence of an apparently distinct syndrome, referred to as mixed connective tissue disease (MCTD) sharing many clinical features of SLE.[58,59,96,97] Whether this condition represents a separate entity or a milder form of SLE is somewhat controversial at this time.[34,98] Nevertheless, there appears to be little question that the clinical course of these four major variants differs notably. Their discrimination therefore becomes clinically important on prognostic and therapeutic grounds. The clinical and serologic features of these lupus-like syndromes are briefly described here and a summary

TABLE 1.—*Incidence of Specific Clinical Features in Four Major Lupus Syndromes—Systemic Lupus Erythematosus (SLE), Discoid Lupus Erythematosus (DLE), Mixed Connective Tissue Disease (MCTD) and Procainamide-Induced Lupus (PIL).*

Clinical Measurements	*SLE (Percent)*	*DLE (Percent)*	*MCTD (Percent)*	*PIL (Percent)*
Arthritis arthralgias ..	77-92	38	96	91
Fever	84-100	6	32	39
Pleuritis	24-57	8	25*	52
Pericarditis	15-45	2		18
Raynaud's phenomenon	6-19	9	84	5
Swollen hands	Rare	0	88	0
Dysphagia	Rare	0	77	0
Myalgia	48	Rare	96	27
Myositis	Rare	0	72	0
Malar rash	40-57	100	15	13
Central nervous system symptoms	26-44	3	0	26
Lymphadenopathy ...	37-68	0	68	9
Splenomegaly	9-41	2	21	5
Hepatomegaly	23-44	0	28	11

References: SLE 99-103; DLE 123-125; MCTD 59, 96, 97; PIL 103, 141, 150, 153.

*Percent having polyserositis.

TABLE 2.—*Incidence of Specific Serologic Abnormalities in Four Major Lupus Syndromes—Systemic Lupus Erythematosus (SLE), Discoid Lupus Erythematosus (DLE), Mixed Connective Tissue Disease (MCTD) and Procainamide-Induced Lupus (PIL)*

Laboratory Measurements	*SLE (Percent)*	*DLE (Percent)*	*MCTD (Percent)*	*PIL (Percent)*
Anemia	57-75	Rare	48	21
Leukopenia	43-65	28	52	33
Thrombocytopenia ..	5-7	5	8	4
Elevated ESR	84	47	80	60
Biological false-positive VDRL ...	22	6	0	0
Antinuclear antibodies*	>95R,D,S	30D	>95S,R	>95D
Positive lupus erythematosus cell ...	76-100	5	20	94
Antibody to ENA ...	55	0	100	?
Antibody to Sm antigen	30-40	?	0	?
Antibody to ds-DNA .	83-100	14-86	12	0
Antibody to ss-DNA .	85-100	50-80	16	50
Antibody to ds-RNA .	70	42	?	12
Hypocomplementemia	90-100	0	0	0
Celluria/proteinuria .	46-70	0	0	0
Abnormal kidney biopsy	95-100	?	?	?
Abnormal skin biopsy†	90/60	95/0	?	90/<5

References: SLE 34, 43, 48, 50, 58, 59, 72-74, 78, 89, 103, 105-114; DLE 123-128; MCTD 34, 59, 96, 97, 107; PIL 130, 141, 150, 153.

*R = rim; D = diffuse; S = speckled.

†Expressed as percent with positive band fluorescence in abnormal skin/percent with positive band fluorescence in uninvolved skin.

of their clinical serologic similarities and differences is presented in Tables 1 and 2.

Systemic Lupus Erythematosus

A great spectrum of symptoms and signs, single or in combination, are currently considered as possible clinical expressions of SLE (Table 1). Although the symptoms reflected in acute, active SLE have changed little from classic earlier descriptions,[99-103] we are currently able to diagnose the disease at a much earlier stage, when it manifests less dramatic signs. We have come to appreciate that this disease is frequently insidious in its onset. Vague constitutional symptoms including low grade fever, weakness, easy fatiguability and weight loss may be the only symptoms. Certain organ systems have a great predilection to become involved in the course of the disease.

The skin, musculoskeletal system and serosal membranes are frequently affected sites. The most common cutaneous feature of SLE is an erythematous rash, often symmetrical, over the face and exposed surfaces of the body. Frequently, the patient reports a diffuse increase in hair loss, and occasionally a history of frank patchy alopecia is elicited. Other skin manifestations may include a characteristic periungual erythema, nonspecific ulcerations of the mucous membranes, erythema nodosum, urticaria and angioedema.

Polyarthralgia or arthritis is typically asymmetric and migratory and may be associated with severe myalgia. Infrequently the arthritis may be severe, symmetric and associated with deformity indistinguishable from rheumatoid arthritis. Very rarely the arthritis may be associated with subcutaneous nodules resembling rheumatoid granulomas. However, the arthritis of SLE is usually very transient and rapidly responds to therapy.

Polyserositis is also common and may take the form of a pleuritis or pleuropericarditis with or without effusion or an underlying pneumonitis. Proliferation of lymphoid tissue may manifest itself in a prominent lymphadenopathy. Splenomegaly and hepatomegaly may also be observed in the active case. Emotional lability, frank psychoses, convulsions, cranial nerve palsies and peripheral neuropathy suggest active CNS lupus. The appearance of peripheral edema coupled with hypertension and an abnormal urinary sediment indicates nephrosis which is observed in 25 percent of patients. In fact, overt nephritis appears to be quite characteristic of SLE, occurring in 60 percent of patients. This distinguishes SLE from DLE, drug-induced variants and mixed connective tissue

disease where overt renal disease generally does not occur.

The incidence of serologic and other laboratory aberrations of classic SLE are summarized in Table 2. Detection of antibodies to a variety of nucleic and cytoplasmic antigens will vary considerably with the diverse techniques employed to measure them.[52,104] Their presence is also dependent on disease activity and whether or not the patient has been actively treated. Since there are no reports quantitating all measurements simultaneously in the same population of untreated patients, the incidence of serologic aberrations summarized in Table 2 should be interpreted as a rough approximation. Several serologic features appear to be extremely useful in delineating patients with classic SLE. Antinuclear antibodies should be detected universally in the serum from untreated lupus patients with active disease if searched for by an indirect fluorescent antibody technique. The patterns of nuclear staining most commonly seen are (1) the rim or shaggy pattern associated with antibodies to either DNA or nucleoprotein, (2) the diffuse pattern associated with antibody to nucleoprotein and (3) occasionally the speckled pattern associated with antibody to Sm antigen or ribonucleoprotein.[58,105-107] Though its sensitivity makes it a useful screening test, a positive result in no way establishes the diagnosis of SLE. The LE cell test is somewhat more difficult to do and is highly dependent on the observer's judgment and skill. Though a positive LE test can occasionally be seen in rheumatoid arthritis, systemic sclerosis and chronic active hepatitis, it carries a greater degree of specificity for SLE. The chances of obtaining a positive initial test in untreated SLE varies between 30 percent and 60 percent. However, over the course of an illness, sequential tests would yield a positive result in nearly every patient.[108] Antibody to ds-DNA associated with hypocomplementemia shows the greatest degree of specificity for SLE.[89,109-113] Recently, it has been demonstrated that the presence of circulating DNA:anti-DNA complexes nearly always represents active disease and persistence of these complexes carries the implication of a poor prognosis.[70,71]

The early evaluation of SLE patients by percutaneous renal biopsy has indicated that few, if any, are free of detectable abnormalities when studied with fluorescent and electron microscopy in addition to light microscopy.[68,73,74] Although virtually nothing is currently known of the histologic status of the kidney in patients with DLE, MCTD or drug-induced equivalents, the absence of urinary sediment or biochemical abnormalities in these patients is in stark contrast to observations in patients with classic SLE. Excluding specific medical contraindications, percutaneous renal biopsy offers an excellent method of establishing the extent of major organ involvement, as well as a definite clue to prognosis.[72,73] Preliminary data suggest that fluorescent studies of skin tissue may mirror, to a large extent, findings in the kidney and may eliminate the risks of renal biopsy in the future.[77] Direct fluorescent antibody studies on clinically normal skin from patients with suspected SLE may be an invaluable tool in establishing the diagnosis. Where 60 percent of normal skin biopsies will be positive for immunoglobulins at the dermal-epidermal junction in SLE, patients with DLE or drug-induced equivalents are invariably negative.[78,114]

A recent report suggested that SLE patients who survived the first five years of disease, experienced greater morbidity and mortality as a result of CNS lupus.[73] Our personal experience certainly supports this observation. Considerable evidence has accumulated to support an immunological mediation of CNS lupus.[79,86,115] However, rapid and accurate discrimination of the neuropsychiatric manifestations of lupus from the behavorial effects of corticosteroids or other frequently employed drugs, metabolic aberrations, infection and cerebral thrombosis, poses a considerable diagnostic problem.[79,80,85,116-118] Antibodies to DNA, DNA:anti-DNA complexes, depressed levels of C4 and decreased concentrations of IgG have been noted in the cerebrospinal fluid of patients with CNS lupus.[71,80-82,115] The availability of such techniques should improve our ability to differentiate active CNS lupus from other possible causes of CNS disturbances in SLE.

Since the original publication of preliminary criteria for the classification of SLE under the auspices of the American Rheumatism Association,[119] their reassessment and clinical application have resulted in suggestions for modification.[120-122] Table 3 lists these criteria; if four of the 14 major criteria are positive, there should be a 98 percent specificity for SLE. A recent report supports the usefulness of these criteria when applied to patients with early SLE and rheumatoid arthritis.[122] The sensitivity of these features was found to be 88 percent with specificity against rheumatoid arthritis at 98 percent. Sensitivity could be in-

TABLE 3.—*Preliminary Criteria for Classification of Systemic Lupus Erythematosus*

1. Facial erythema (Butterfly Rash)
2. Discoid lupus
3. Raynaud's phenomenon
4. Alopecia
5. Photosensitivity
6. Oral or nasopharyngeal ulceration
7. Arthritis without deformity. (One or more peripheral joints involved with any of the following in the absence of deformity—(a) pain on motion, (b) tenderness, (c) effusion or periarticular soft tissue swelling)
8. Lupus erythematosus cells
9. Chronic false-positive standard test for syphilis
10. Profuse proteinuria
11. Cellular casts
12. One or both of the following—(a) pleuritis, (b) pericarditis
13. One or both of the following—(a) psychosis, (b) convulsions
14. One or more of the following—(a) hemolytic anemia, (b) leukopenia, (c) thrombocytopenia

creased to 92 percent, without loss of specificity, when increased titer of antinuclear antibodies was employed as an alternative to the LE cell test. These criteria do not require sophisticated serologic tests and should serve as a practical universal guideline for diagnosis.

Discoid Lupus Erythematosus

The relationship between DLE and SLE has intrigued clinicians for years, not only on theoretic grounds, but also for diagnostic reasons. Based on sex incidence (2:1 male to female ratio), clinical symptomatology (Table 1), laboratory findings (Table 2), as well as a more favorable prognosis, the two conditions must be considered separate, though undoubtedly closely related.[123,124] Clinically, DLE is characterized by cutaneous lesions which consist of well-defined red to violaceous papules and plaques with somewhat elevated active borders and scaly, paler centers. As the lesions mature, atrophy and scarring appear in their centers and telangiectasis is occasionally observed in atrophic areas. These lesions can be localized or widespread over various parts of the body. Rothfield and associates compared patients with chronic DLE with matched controls and found that systemic disease was observed in only a small number of the former.[125] Polyarthralgia is a clinical feature in a third of these patients.

More than one-half of DLE patients have some laboratory abnormalities commonly associated with SLE.[126,127] Although anemia and thrombocytopenia are infrequent, leukopenia has been noted in approximately 25 percent of DLE patients. The erythrocyte sedimentation rate is frequently elevated and nearly a third of DLE patients have antinuclear antibodies usually manifesting a diffuse pattern on fluorescent studies. Though it has been stated that DLE patients with antinuclear antibodies run the same risk of developing SLE as those who are seronegative,[126] studies employing sensitive assays for ds-DNA support the predictive value of increased levels of antibody to ds-DNA and subsequent development of SLE.[127] Though patients with DLE may demonstrate increased levels of antibody to ds-DNA, it is never associated with hypocomplementemia. Recent studies have demonstrated circulating antibody to ds-RNA in 42 percent of patients with DLE as compared with 70 percent in SLE.[128] The latter together with the observations of circulating anti-ds-DNA antibody[127] substantiate the fact that DLE is a part of the SLE spectrum. In fact, a small proportion of DLE patients, about 5 percent, go on to develop overt SLE.[123-125]

Of major prognostic and therapeutic importance are the absence of renal and CNS involvement and favorable responses to local steroid therapy or antimalarial compounds or both. Diagnostically, a useful distinguishing feature is the complete absence of immunoglobulin deposition at the dermal-epidermal junction in uninvolved skin when studied by fluorescent microscopy.[78]

Though the issue of its precise relationship to SLE must remain unsettled, considerable agreement exists to support the contention that DLE is to a large degree a cutaneously expressed aberration capable of remaining confined to this organ indefinitely.[124-126] Therapeutic endeavors must be tempered accordingly and discriminating DLE from SLE becomes highly important.

Mixed Connective Tissue Disease

Over the past decade, studies by Sharp and his colleagues led to the description of a group of patients whose clinical syndrome suggested the coexistence of several autoaggressive disorders (SLE, systemic sclerosis and polymyositis). The syndrome was termed mixed connective tissue disease (MCTD).[58,59,96,97] Patients with this syndrome resemble those with SLE as they suffer a high incidence of polyarthralgias and non-deforming arthritis, may have recurrent difficulties with polyserositis and occasionally manifest typical cutaneous lesions (Table 1). Lymphadenopathy and

hepatosplenomegaly are seen to a similar degree as in SLE. MCTD differs clinically from classic SLE due to the high incidence of swollen, sclerodermatous-like hands, dysphagia with abnormal esophogeal motility, Raynaud's phenomenon and an active myositis. Cutaneous changes typical of dermatomyositis are occasionally seen over the eyelids and metacarpal-phalangeal joints. CNS symptoms are not a feature of this entity. Prognostically the course is usually mild with characteristically excellent response to corticosteroids.

The serologic findings common to all patients with MCTD are (1) high titers of antinuclear antibody giving a speckled (infrequently, rim) pattern on fluorescent testing, (2) high titers of antibody to ENA with specificity to the nuclear RNA protein, Mo, (3) no detectable antibody to Sm antigen, (4) relative infrequency of antibody to ds-DNA and ss-DNA and (5) normal or elevated levels of serum complement (Table 2). Furthermore, there is a paucity of renal involvement as determined by urinalysis and glomerular filtration rate. It must be pointed out, however, that a systematic study of renal tissue has not been reported. Similarly, fluorescent microscopic studies of skin tissue and their relationship, if any, to other lupus variants is not currently known.

Recently a subgroup of SLE patients, reported by Reichlin and Mattioli, were noted to have serologic features similar to patients with MCTD.[98] Sera from these patients contained antibody to RNA protein and had a low incidence of anti-DNA antibody. Furthermore, there was a paucity of renal disease and their favorable clinical course set them apart from other patients with SLE. This SLE subgroup differed from those with MCTD with respect to the predominant clinical features so frequently seen in the latter. Hence, there is some controversy as to whether the clinical and serologic features ascribed to MCTD warrant the creation of a separate disease entity. It may be more appropriate to distinguish these patients as a specific segment of the obviously heterogeneous SLE community who have immunologic features consistent with a more favorable prognosis. In this respect, it has been suggested that antibody to ENA may exert a protective effect by inhibiting the formation or consequences of DNA:anti-DNA complexes.[59,97] There is some supportive experimental evidence for this hypothesis in the murine lupus model. Weekly injections of ENA were observed to have an inhibiting effect on the induction of renal disease when compared to untreated controls.[129]

TABLE 4.—*Drugs Implicated in the Induction of a Lupus-Like Syndrome*

Procainamide[130,131]	Penicillamine[140]
Hydralazine[132]	Oral contraceptive agents[141,142]
Isoniazid[133]	Phenothiazines[143]
Sulfonamides[134]	Quinidine[144]
Penicillin[135]	Ethosuximide[145]
Tetracycline[136]	Phenylbutazone[146]
Streptomycin[137]	Diphenylhydantoin[147]
p-Aminosalicylic acid[138]	Mephenytoin[148]
Griseofulvin[139]	Trimethadione[149]

Irrespective of whether one agrees with the validity of a separate clinical entity, MCTD or simply a milder form of SLE, it appears certain that some patients with a lupus variant can be discriminated by well-defined serologic and to some degree, clinical, features. These persons rarely manifest either the renal or the CNS complications of SLE, respond briskly to corticosteroid therapy and generally enjoy a more favorable prognosis.

Drug-Induced Lupus

The drugs reported as capable of inducing a lupus-like syndrome, antinuclear antibodies and LE cell test positivity are listed in Table 4. The implication is most convincing for hydralazine and procainamide; and somewhat less so for isoniazid, diphenylhydantoin, mephenytoin and tridione. Most of the other drugs have been reported causing a lupus-like syndrome only sporadically, and their true relationship, in many instances, remains controversial. Pathogenetically, a better understanding of the drug-induced equivalent may be the key to the trigger mechanisms of autoimmunization.

Among the drug-induced syndromes, procainamide and hydralazine appear to initiate different entities and may represent two broad categories of disease. Procainamide triggers a lupus-like syndrome which frequently subsides when the drug is discontinued. Most patients with PIL have no personal or family history of a rheumatic disorder. Hydralazine produces a similar disorder which appears to occur more often in patients with an underlying diathesis. The incidence of a personal or family history of a rheumatic disorder in this group is 74 percent.[150] Its manifestations persist in a higher percentage of patients than with the procainamide-induced form.[150] Patients with active hydralazine lupus develop circulating antibodies to hydralazine, and their lymphocytes undergo blast transformation to hydralazine *in*

vitro.[151] All patients in whom hydralazine lupus develops are slow acetylators of the drug.[152] Patients with hydralazine-induced lupus are similar to those with SLE; sera from these patients contains antibodies to both ds-DNA and ss-DNA. The clinical and other serologic features of hydralazine lupus resemble those of procainamide-induced lupus (PIL) tabulated in Tables 1 and 2.

Currently, procainamide appears to be the most recognized offender in the induction of lupus. Of patients receiving the drug for an appreciable length of time, 75 percent develop antinuclear antibodies, usually with a diffuse pattern of fluorescence.[153] A small percentage of these patients develop a lupus-like reaction characterized by polyarthralgia, myalgia, fever and pleurisy (Table 1).[131,132,150,153] As with DLE, the preponderance of males affected is in striking contrast to that seen in SLE. Renal and CNS disease are notably absent. The latter has been attributed to a lack of complement-fixing antibodies to ds-DNA. Antibodies to ss-DNA are seen in 50 percent of clinically affected cases. Positive LE cell preparations are very common. It has been suggested that as a result of photo-oxidation, procainamide may combine with DNA and various other nuclear macromolecules to render these substances immunogenic.[131]

Cessation of procainamide is followed by abatement of symptoms within a period of two to three weeks. Occasionally, manifestations of lupus may persist for prolonged periods ranging from 5 to 49 months after the medication is stopped.[150] When necessary, corticosteroids may be employed briefly, and almost universally result in prompt clinical improvement.

Course and Treatment of SLE

A recent study emphasizing the relationship of racial factors and mortality indicated that 62.7 percent of blacks and 64.4 percent of whites had survived after five years of disease.[1] Moreover, the data indicated that the most critical years for survival are the first three or four after diagnosis. In one segment of a New York City population, the fatality was 15.5 percent in the first year, about 8 percent annually in the next three years and from 1 to 5 percent each year thereafter. Various racial groups were comparable in respect to therapy and involvement of major organ systems. It was concluded that ethnic differences were not detectable in survival rates despite racial variations in susceptibility to the disease.

The effect of pregnancy on survival was also studied and indicated that the estimated five year survival rate (ranging between 50 and 54 percent) was lowest for nonpregnant women. For those with one pregnancy after diagnosis, the probability of surviving five years was 80 percent. Differences in outcome could not be explained on the frequency of renal or CNS involvement alone, since these were comparable but depended on the severity of disease at the time of conception and the degree of activation of the disease during gestation and the puerperium.[1]

Dubois and his associates recently reviewed the causes of death in 212 patients with SLE with emphasis on 89 patients in whom autopsies had been done.[154] Uremia continued to be the leading cause of death (28 percent) with CNS complications (15 percent), infection (8 percent) and malignancy (4 percent) also playing important roles. As is often the case, multifactorial causes accounted for fatality in 10 percent of cases. The dramatic decrease in CNS complications as well as the significant decrease in uremia as a cause of death was attributed to earlier and more frequent employment of corticosteroids. On the other hand, there was a notable increase in the rate of infections, vascular complications and malignancy in the patient segment studied. It is tempting to ascribe many of these fatal complications to corticosteroids. However, a recent study comparing patients with SLE, rheumatoid arthritis and nephrotic syndrome suggested that the increased infection rate in SLE cannot be attributed to steroid therapy and decreased renal function alone.[155] From what is suspected regarding its fundamental causes (Figure 1), the relationship, if any, between the increased rate of malignancy in patients with SLE and any prior therapy should be interpreted with care. As the rate of survival increases, the rate of malignancy might also be expected to rise on theoretical grounds proportional to the degree of persistent viral infection and depressed cell-mediated immunity.

In that a specific curative agent is not known, the quality and intensity of therapy is highly dependent on the patient's clinical features. Since three of the four variants discussed above are either self-limited or easily controlled with conservative corticosteroid treatment, complete patient evaluation must precede long-term therapeutic decisions.[156-158] General measures including good nutrition and avoidance of sunlight are important considerations in the management of SLE. Salicylates may be effective when the major mani-

festations consist of mild polyarthritis or polyserositis. In this respect, the clinician should be cognizant of the recent association of aspirin and hepatitis, particularly in patients with SLE.[159] Nonsteroidal anti-inflammatory drugs such as indomethacin may be of benefit when salicylates fail to adequately control musculoskeletal complications.

Once it is determined that an individual patient has acute multisystem SLE, prednisone should be administered in daily doses of 60 mg or more until clinical manifestations have subsided. With satisfactory remission of the disease, the dose of corticosteroids can be slowly and carefully tapered. If control cannot be achieved with dose levels below 15 mg of prednisone daily, the addition of an immunosuppressive drug should be considered.

Diffuse proliferative nephritis characterized by extensive subendothelial deposits, as well as membranous glomerulonephritis, usually requires long-term employment of large doses of steroids before adequate control can be achieved. The myriad of problems attendant with long-term use of corticosteroids and the frequent failure of these renal complications to respond adequately has resulted in the introduction of a variety of immunosuppressive agents as treatment modalities.[156,160-164] Guidelines for the use of such agents have been published.[165,166] Although some controversy still exists,[167,168] there is an impressive body of controlled and uncontrolled data supporting the efficacy of azathioprine and prednisone,[160,163,164,169,170] cyclophosphamide and prednisone,[161,162,170-172] and chlorambucil and prednisone[173] in the treatment of lupus nephritis. Our experience indicates that the best therapeutic responses are achieved by administering low doses of prednisone (10 to 20 mg daily), together with 2 to 2.5 mg per kilogram of azathioprine daily. Upon achieving remission, the prednisone is initially withdrawn slowly. Although a gradual withdrawal of azathioprine is also desirable, many patients may require a minimal dose (such as 50 mg daily) to maintain their disease in a state of remission. The use of these agents appears to reduce, and in some cases, completely avoid the undesirable consequences of long-term treatment with corticosteroids.[169] As with corticosteroids, rapid withdrawal of these immunosuppressive drugs may induce an acceleration of disease, and whenever possible, a gradual reduction is preferred.[169-174]

The value of corticosteroids in the treatment of the neurologic complications of SLE is uncertain. Although dramatic improvement following their use has been observed, there are many patients who fail to respond or worsen during such therapy.[79,80] The psychiatric complications of steroids are frequently difficult to discriminate from the neuropsychiatric manifestations of SLE, frequently posing a therapeutic dilemma which must be resolved clinically for each patient.[175]

There is little doubt as to the vast improvement which has taken place in the prognosis of SLE in recent years. Five-year survivals of nearly 80 percent are currently being reported, even in renal-complicated SLE.[173] This is based not only on an earlier diagnosis, but also on the beneficial effects of corticosteroids and other immunosuppressive agents. The disease no longer poses its formerly serious threat to survival provided that aggressive measures are taken to abrogate serious damage to vital organs. As noted above, early evaluation of renal tissue as well as complement and DNA antibody studies can provide useful information in assessing the course of patients with renal involvement, as well as identifying those who are more likely to develop critical functional impairment.

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